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Original article

Anti-tubercular agents. Part 7: A new class of diarylpyrrole–oxazolidinone conjugates as antimycobacterial agents

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ABSTRACT

In an effort to discover new anti-tubercular agents, a series of new diarylpyrrole–oxazolidinone conjugates have been designed and synthesized. The anti-tubercular activity of these new conjugates (**4a**–**n** and **5a**–**d**) against *Mycobacterium tuberculosis* $H_{37}Rv$ and drug resistance strains such as *M. tuberculosis* Rif^R and *M. tuberculosis* XDR are discussed, wherein compound **4i** has been found to be the most potent amongst the series. MTT assay was performed on the active conjugates of the series (**4b**–**f**, **4i** and **5c**) against mouse macrophage (J-774) cells to evaluate cytotoxic effects and selective index values. In addition, these conjugates (**4a**–**n** and **5a**–**d**) are also tested against a panel of Gram-positive and Gram-negative bacterial strains. The docking studies have been carried out to provide some insight into the mechanism of action for this class of compounds.

1. Introduction

Despite the availability of efficacious treatment and diagnosis for tuberculosis (TB), caused by the bacillus *Mycobacterium tuberculosis* (MTB), TB still remains a major health problem. In 1993, the World Health Organization (WHO) declared TB as a global emergency [1]; at that time when an estimated 7–8 million cases and 1.3–1.8 million deaths occurred each year. In 2010, there were an estimated 8.8 million cases of TB, 1.1 million deaths among HIV-negative cases of TB and an additional 0.35 million deaths among people who were HIV-positive [2]. Inspite of improved sanitation, better lifestyle and the widespread use of the bovine Calmette–Guerin vaccine, MTB still persists as a leading bacterial infection problem [3,4]. The efficacy of currently available drugs used in standard tuberculosis treatment regimen is seriously limited by several factors: including HIV-1 infection, long treatment regimens and multiple drug treatment regimens [5,6]. Moreover, the increasing emergences of drug resistant TB, especially multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) are particularly alarming [7,8]. There has been an increase in the number of TB patients diagnosed with MDR-TB in the last five years.

For the first time in 40 years, there is a coordinated portfolio of promising new drugs on the horizon. There are 10 new or repurposed TB drugs in trials, which have the potential to shorten the treatment of drug-susceptible TB and to improve the treatment of multidrug-resistant TB. Some notable examples that are under different stages of clinical trials include gatifloxacin (**1a**), moxifloxacin (**1b**), levofloxacin (**1c**) and linezolid (**2a**) as shown in Fig. 1 [1,9]. Linezolid is the first and only oxazolidinone which is effective for the treatment of Gram-positive bacteria including first-line drug resistance infections in humans and recently has been suggested as an alternative treatment for patients infected with *M. tuberculosis* isolates [10–12]. The oxazolidinones, represent a new class of synthetic antibacterial agents that emerged in the last four decades having potent activity against multidrug-resistant Gram-positive bacteria. Oxazolidinones target the bacterial protein synthesis prior to the chain initiation step by binding to the 23S rRNA of 50S ribosomal subunit and interfering with the initiator fMET-rRNA binding to the P-site of the ribosomal peptidyltransferase center [13,14]. Many efforts have been made on developing new

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oxazolidinones toward extending the spectrum of activity and reducing the toxic effects. Recent studies have shown that the conversion of the acetamide group of linezolid to the triazolyl, example PH-027 (**2b**) as shown in Fig. 1 could restore its antibacterial activities [15–18]. On the other hand, diarylpyrroles were first reported by Biava and coworkers as antimycobacterials and amongst them BM212 (**3**) is the most potent derivative which showed promising activity toward several strains of MTB [19,20].

In an effort to global fight against tuberculosis, from our laboratory many series of compounds have been designed and synthesized that exhibit promising antimycobacterial activity and some are undergoing detailed investigations [21–23]. In the present investigation we have introduced a new class of diarylpyrrole–oxazolidinone conjugates as potential antimycobacterial agents. In this context the diarylpyrrole group has been attached to (*R*)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-5-((4-aryl/heteroaryl-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one at the distal piperazine N–H position in order to identify new molecules with improved antimycobacterial activity. Additionally, phenyl, *m*-tolyl, 2-pyridyl and 1*H*-methyl-5-imidazolyl groups have been introduced at the 4th position of the 1*H*-1,2,3-triazole ring. Attempts have also been made to correlate the structure to antimycobacterial activity of these compounds.

2. Chemistry

The synthetic pathways employed for the generation of different products in the series are described in Schemes 1 and 2. Various substituted diarylpyrroles have been prepared from the corresponding 1,4-diketones and anilines. Synthesis of diarylpyrroles is depicted in Scheme 1, wherein the reaction of a suitable benzaldehyde with methyl vinyl ketone, under Stetter conditions to yield 1,4-diketones (**8a**–**f**) [20], followed by modified Paal–Knorr condensation procedure using $Gd(OTf)_3$ as catalyst. In the Paal–Knorr condensation, the intermediates (**8a**–**f**) were treated with the appropriate amines in the presence of $Gd(OTf)_3$ for cyclization to yield the required diaryl pyrroles (**9a**–**h**) in good yields.

The key intermediate (*S*)-*N*-[[3-(3-fluoro-4-(piperzinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]-azide (**10**) has been synthesized as previously described [24,25]. The union of these two fragments (**9a**–**h**) and **10** was achieved by employing Mannich reaction between them to produce **11a**–**h** (Table 1). The azido compounds (**11a**–**h**), thus obtained were then converted to diarylpyrrole–triazolyloxazolidinone conjugates (**4a**–**n**) by click chemistry using aryl/heteroaryl acetylenes in the presence of copper sulfate and catalytic amount of sodium ascorbate in *t*-BuOH and water (3:1) as illustrated in Scheme 2 [26,27].

In addition, the diarylpyrrole–oxazolidinone conjugates (**5a**–**d**) were prepared as outlined in Scheme 2. The amino compounds **12a**–**d** were obtained from the reduction of azide group of **11a**, **11b**, **11f** and **11h** in the presence of ammonium formate and catalytic amount of zinc dust in methanol (Table 1). On acylation of the amino compounds (**12a**–**d**) in the presence of acetyl chloride in dry CH_2Cl_2 employing triethylamine as a base, the corresponding acetamides were obtained (**5a**–**d**).

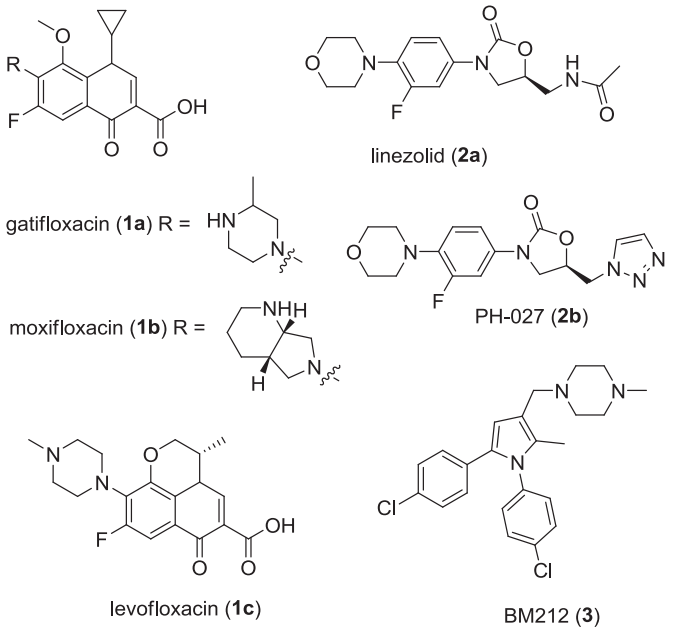


Fig. 1. Potent anti-tubercular agents and antibacterial agents.

3. Results and discussion

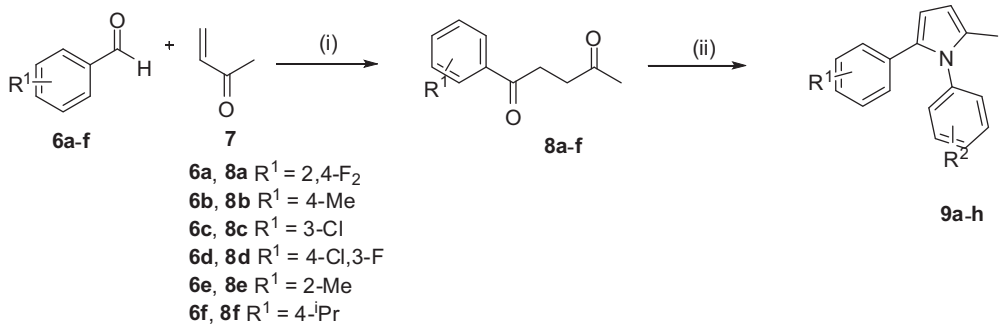
3.1. Antimycobacterial activity

These newly synthesized diarylpyrrole–oxazolidinones (**4a**–**n** and **5a**–**d**) were evaluated for their antimycobacterial activity against *M. tuberculosis* isolates using the microplate dilution assay at 1–16 μg/mL concentrations. The drugs in clinical use rifampicin and linezolid were used as reference compounds. The *in vitro* test results for this new class of compounds are outlined in Table 2 as minimum inhibitory concentration (MIC) and the activity ranges from 2 to >6.25 μg/mL. Moreover, these compounds have also been screened against *M. tuberculosis* Rif^R and *M. tuberculosis* XDR. At primary screening, the compounds **4a**–**d**, **4e**–**i** and **5a**–**c** showed significant inhibition against MTB. Amongst the evaluated conjugates, the conjugate (5*R*)-3-(3-fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-*o*-tolyl-1*H*-pyrrol-3-yl)methyl)piperazin-1-yl)phen-yl)-5-((4-(1-methyl-1*H*-imidazol-5-yl)-1*H*-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4i**) was found to be more active against MTB (2 μg/mL) compared to the other compounds in this series. Moreover, compound **4i** exhibited very good activity against the resistant strains such as, rifampicin resistant MTB (4 μg/mL) and XDR-TB (8 μg/mL).

In the structure activity relationship (SAR) studies, some interesting trends have been observed in these conjugates. In the substituted triazole series, the conjugates having pyridyl group (**4a**–**e**) and 1-methyl-1*H*-imidazol-5-yl group (**4f**–**i**) at 4-position of triazole ring have shown promising activity (2–16 μg/mL) compared to the compounds having phenyl/*m*-tolyl group at 4-position of triazole ring (**4j**–**n**). This observation indicates the importance of the presence of 2-pyridyl/1-methyl-1*H*-imidazol-5-yl group (**4f**–**i**) at 4-position of the triazole ring which is playing key role in exhibiting the activity against *Mycobacterium*. Compounds **5a**–**d** that possess a C5-acetamide group as in case of linezolid also showed moderate activity against *M. tuberculosis* (4–16 μg/mL).

3.2. Cytotoxicity assay

As described in experimental procedure, the maximum tolerated test (MTT) was performed to evaluate the *in vitro* cytotoxicity of the promising compounds (**4b**–**f**, **4i** and **5c**) against mouse macrophage (J-774) cell lines. These compounds were not cytotoxic as indicated by their IC_{50} values. The IC_{50} and selective index (SI) values of these compounds are shown in Table 3. The good selectivity index values for these compounds indicate its potential usefulness in the drug development for tuberculosis.

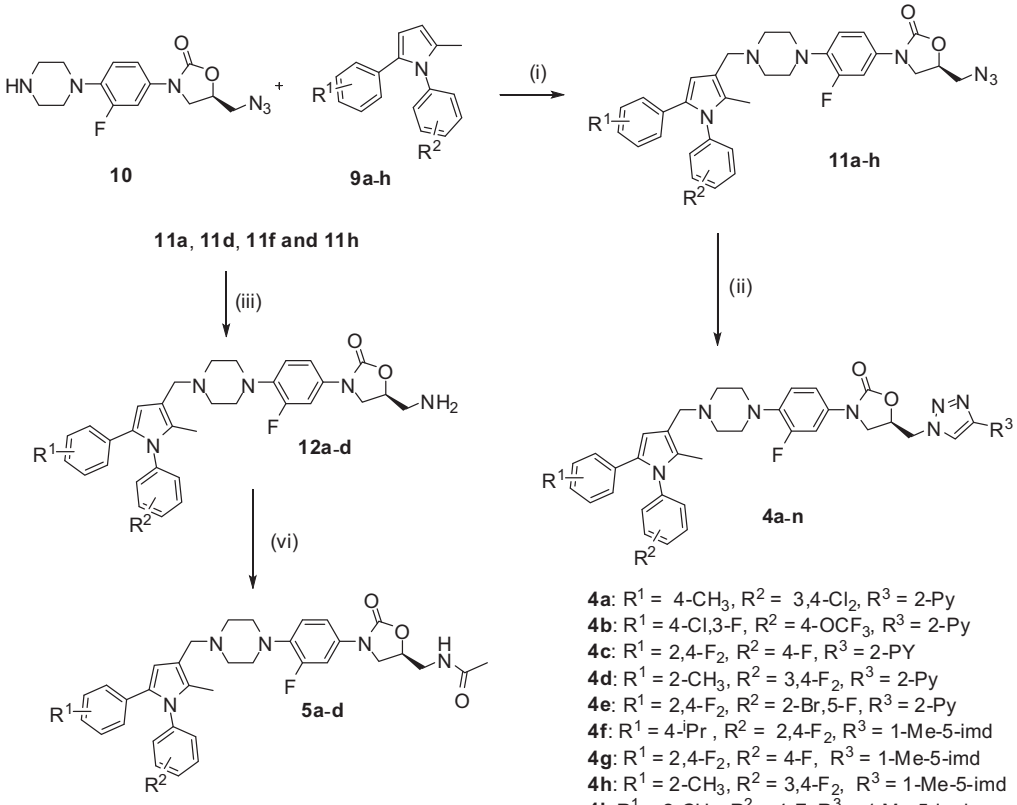


Scheme 1. Synthesis of substituted diarylpyrroles (**9a**–**h**): *Reagents and conditions*: (i) 1,3-ethyl-5-(2-hydroxyethyl)-4-methyl-thiazolium bromide, NEt_3, 75–78 °C, 5 h, 2N HCl; (ii) R^2-NH_2, cat. $Gd(OTf)_3$, 30 °C, 30 min.

3.3. Antibacterial activity

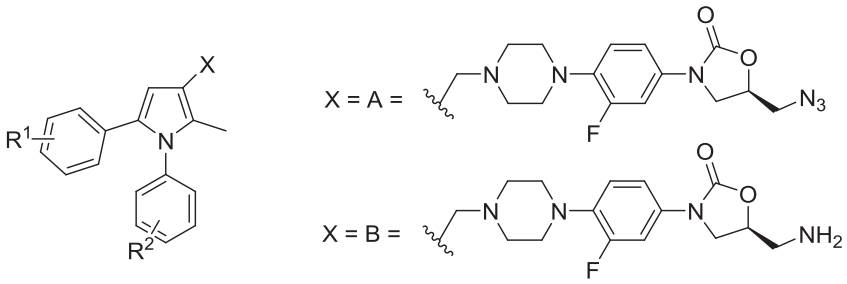
These compounds have also been evaluated for their antibacterial activity against a panel of Gram-positive and Gram-negative pathogens and compared with linezolid as a reference antibacterial. The antibacterial evaluation of the compounds reported as the minimum inhibitory concentrations (MICs, μg/mL) determined by the agar dilution method on Mueller–Hinton (HM) agar is summarized in Table 4. It is observed from the results that some of the conjugates show good antibacterial activity against Gram-positive organisms and insignificant activity against Gram-negative organisms.

Conjugates like **4a**–**d**, **4f**, **4j**–**l** and **5a**–**d** that showed significant activity in the primary screening against Gram-positive bacteria. Then these were further evaluated at different concentrations to find MICs and the results are outlined in Table 4. Compounds **4c** and **5b** are found to be most active against *Staphylococcus aureus* MTCC 96 (MIC 0.5 μg/mL), whereas compound **4l** was active against *Micrococcus luteus* MTCC 2470 with MIC 0.5 μg/mL. These compounds showed very good inhibitory zone (12–40 mm) when



Scheme 2. Synthetic route of diarylpyrrole–triazolyl oxazolidinone conjugates (**4a**–**n** and **5a**–**d**): *Reagents and conditions*: (i) HCHO, cat. ACOH, CH_3CN, 0 °C–rt, 6 h; (ii) aryl/heteroaryl acetylenes, $CuSO_4$, cat. Sodium ascorbate, t-BuOH + H_2O (3:1), 4 h; (iii) Pd/C, H_2 gas, EtOH, rt, 3 h; (iv) acetyl chloride, TEA, dry DCM, 0 °C–rt, 1 h.

Table 1
Structural interpretation of the compounds **9a**–**h**, **11a**–**h** and **12a**–**d**.



Entry	Compd	R_1	R_2	X
1	**9a**	2,4-F_2	2-Br,5-F	H
2	**9b**	2,4-F_2	4-F	H
3	**9c**	4-CH_3	3,4-Cl_2	H
4	**9d**	3-Cl	2-F	H
5	**9e**	4-Cl,3-F	4-OCF_3	H
6	**9f**	4-^{i}Pr	2,4-F_2	H
7	**9g**	2-CH_3	3,4-F_2	H
8	**9h**	2-CH_3	4-F	H
9	**11a**	2,4-F_2	2-Br,5-F	A
10	**11b**	2,4-F_2	4-F	A
11	**11c**	4-CH_3	3,4-Cl_2	A
12	**11d**	3-Cl	2-F	A
13	**11e**	4-Cl,3-F	4-OCF_3	A
14	**11f**	4-^{i}Pr	2,4-F_2	A
15	**11g**	2-CH_3	3,4-F_2	A
16	**11h**	2-CH_3	4-F	A
17	**12a**	2,4-F_2	2-Br,5-F	B
18	**12b**	3-Cl	2-F	B
19	**12c**	4-^{i}Pr	2,4-F_2	B
20	**12d**	2-CH_3	4-F	B

compared to standard reference drugs (Table 5). Compounds with pyridyl group at 4-position of triazole ring (**4a**–**d**) and compounds with C5-acetamide group (**5a**–**d**) displayed enhanced activity against Gram-positive strains. On the other hand, the moieties that have 1-methyl-1*H*-imidazol-2-yl group at 4-position of the triazole ring (**4f**–**i**) showed lower activity against Gram-positive strains. Interestingly, compounds with phenyl group at 4-position of triazole ring (**4j**–**l**) were active against Gram-positive organisms.

3.4. Docking studies in 50S unit of ribosome

To provide some insight into the mechanism of action for this class of compounds, the docking studies have been carried out. The basic scaffold of diarylpyrrole–oxazolidinone conjugates (**4a**–**n** and **5a**–**d**) is similar to that of the linezolid, a drug candidate from oxazolidinone class. Hence these molecules are expected to bind to the 50S unit of the ribosome similarly to that of the linezolid. Docking studies of the selected conjugates (**4a**–**c**, **4f**, **4i**, **4l**, **5a**, **5c** and **5d**) were performed using Gold docking software. The docking studies were performed to get further insight for the binding mode of the molecules in the 50S unit of the ribosome and the fitting scores of all the compounds (**4a**–**c**, **4f**, **4i**, **4l**, **5a**, **5c** and **5d**) were listed in Table 6. Docking studies revealed that the binding mode is the hydrogen bonding interactions with G2540. For all the tested molecules, docking scores were in the range of the co-crystal ligand linezolid. The binding pose for the molecule **4i** in 50S unit of ribosome was shown in Fig. 2.

4. Conclusion

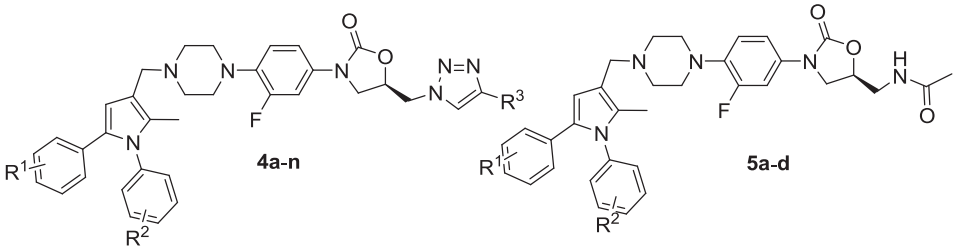
In the present investigation, we have designed and synthesized a new class of diarylpyrrole–oxazolidinone conjugates. The antimycobacterial activities of these compounds are evaluated and correlated with the structures. These novel oxazolidinone conjugates have shown significant antimycobacterial activity against *M. tuberculosis* H_{37}Rv and promising activity against *M. tuberculosis* Rif^R and *M. tuberculosis* XDR strains. Furthermore, the MTT assay performed on these conjugates confirms that these molecules have no cytotoxic effect and possess good selective index values. Amongst the new oxazolidinones, **4i** is found to be the most active derivative and will be taken up for lead optimization to design novel antitubercular agents. In addition, some of the new compounds such as **4c**, **5a** and **5d** have shown good activity against a panel of Gram-positive organisms. Docking studies revealed that the binding mode is the hydrogen bonding interactions with G2540 in the 50S unit of the ribosome. The active conjugates have shown good docking scores, which were in the range of the co-crystal ligand linezolid. Further investigations on this oxazolidinone scaffold are ongoing in our laboratory with a view to develop improved antimycobacterial agents.

5. Experimental protocols

5.1. General

All chemicals were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) or Spectrochem Pvt. Ltd (Mumbai, India) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (200 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts are reported in parts per million (δ in ppm) relative to the peak for

Table 2
Anti-tubercular activity of the compounds (**4a**–**n** and **5a**–**d**) against *Mycobacterium tuberculosis* $H_{37}Rv$ and clinical isolates.



Compd	R^1	R^2	R^3	*M. t*[a]	*M. t*[b]	*M. t*[c]
4a	4-CH_3	3,4-Cl_2	A	4.0	4.0	16.0
4b	4-Cl,3-F	4-OCF_3	A	4.0	4.0	>16.0
4c	2,4-F_2	4-F	A	4.0	8.0	16.0
4d	2-CH_3	3,4-F_2	A	4.0	4.0	16.0
4e	2,4-F_2	2-Br,5-F	A	NT	NT	NT
4f	4-^{i}Pr	2,4-F_2	B	4.0	8.0	4.0
4g	2,4-F_2	4-F	B	>6.25	8.0	16.0
4h	2-CH_3	3,4-F_2	B	>6.25	8.0	>16.0
4i	2-CH_3	4-F	B	**2.0**	**4.0**	**8.0**
4j	4-Cl,3-F	4-OCF_3	C	>16.0	>16.0	>16.0
4k	4-CH_3	3,4-Cl_2	C	>16.0	>16.0	>16.0
4l	2,4-F_2	2-Br,5-F	C	>16.0	>16.0	>16.0
4m	2-CH_3	4-F	C	>16.0	>16.0	>16.0
4n	2-CH_3	4-F	D	>16.0	>16.0	>16.0
5a	2,4-F_2	2-Br,5-F	–	8.0	8.0	>16.0
5b	3-Cl	2-F	–	8.0	8.0	>16.0
5c	4-^{i}Pr	2,4-F_2	–	4.0	4.0	16.0
5d	2-CH_3	4-F	–	NT	NT	NT
Rif				0.2	>128	2.0
LZ				1.0	2.0	4.0

A = 2-pyridyl; B = 1-methyl-1*H*-imidazol-5-yl; C = phenyl; D = *m*-tolyl; the tests were performed in duplicate and repeated thrice; LZ (Linezolid); AT-B (Amphotericin); NT (Not Tested). Bold represents MIC values of the active compounds.
[a] *M. t* (*Mycobacterium tuberculosis* $H_{37}Rv$).
[b] *M. t* (*Mycobacterium tuberculosis* Rif^R).
[c] *M. t* (*Mycobacterium tuberculosis* XDR-1).

tetramethylsilane (TMS) as an internal standard, coupling constants are reported in Hertz (Hz). Spectral patterns were designated as s, singlet; d, doublet; dd, double doublet; t, triplet; bs, broad singlet; m, multiplet. ESI spectra were recorded on Micromass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}.

5.2. Preparation of the compounds ***9a–h***

5.2.1. 1-(2-Bromo-5-fluorophenyl)-2-(2,4-difluorophenyl)-5-methyl-1H-pyrrole (***9a***)

To a solution of 1-(2,4-difluorophenyl) pentane-1,4-dione (**8a**, 254 mg, 1.2 mmol) in acetonitrile (3 mL), 2-bromo-5-fluorobenzenamine (190 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. After completion of reaction as indicated by TLC, water (10 mL) was added to the reaction mixture and extracted by using ester. The product was purified by column chromatography by using hexane, ethyl acetate (10:1) system gives the product (**9a**) (yield 351 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.39 (d, 1H, J = 2.9 Hz, Ar–*H*), 7.34 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.22 (d, 1H, J = 2.9 Hz, Ar–*H*), 7.02 (s, 1H, Ar–*H*), 6.85 (s, 1H, Ar–*H*), 6.21 (d, 1H, J = 3.4 Hz, pyr–*H*), 5.97 (d, 1H, J = 3.4 Hz, pyr–*H*), 2.06 (s, 3H, pyr–CH_3); ESIMS: m/z 366 $(M + H)^+$.

Table 3
IC_{50} (μM) and selectivity index (SI) values of active compounds (**4b**–**f**, **4i** and **5c**) against mouse macrophage cell lines (J-774).

Entry	Compound	MIC (μg/mL) in *M. tb* $H_{37}Rv$	% cell inhibition at 40 μg/mL	IC_{50} approximation	SI index IC_{50}/MIC
1	**4b**	4.0	37.7	>40	>10
2	**4c**	4.0	31.9	>40	>10
3	**4d**	4.0	40.0	>40	>10
4	**4e**	4.0	43.9	>40	>10
5	**4f**	4.0	44.7	>40	>10
6	**4i**	4.0	49.3	>40	>10
7	**5c**	4.0	40.2	>40	>10

5.2.2. 2-(2,4-Difluorophenyl)-1-(4-fluorophenyl)-5-methylpyrrole (***9b***)

The compound **9b** was prepared according to the above-described method using 1-(2,4-difluorophenyl)-1,4-pentanedione (**8a**, 254 mg, 1.2 mmol) and 4-fluoroaniline (111 mg, 1.0 mmol) (yield 275 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10–6.97 (m, 5H, Ar–*H*), 6.73–6.62 (m, 2H, Ar–*H*), 6.28 (d, 1H, J = 3.7 Hz, pyr–*H*), 6.09 (d, 1H, J = 3.7 Hz, pyr–*H*), 2.12 (s, 3H, pyr–CH_3); ESIMS: m/z 288 $(M + H)^+$.

5.2.3. 1-(3,4-Dichlorophenyl)-2-methyl-5-p-tolyl-1H-pyrrole (***9c***)

The compound **9c** was prepared according to the above-described method using 1-*p*-tolylpentane-1,4-dione (**8b**, 228 mg, 1.2 mmol) and 3,4-dichlorobenzenamine (162 mg, 1.0 mmol) (yield 302 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, 2H, J = 3.1 Hz, Ar–*H*), 7.03 (t, 2H, J = 2.2 Hz, Ar–*H*), 7.00 (t, 2H, J = 2.2 Hz, Ar–*H*),

Table 4
Antibacterial activity of the compounds (**4a**–**n** and **5a**–**d**) against several standard strains.

Compd	*S. aureus*[a]	*S. MLS − 16*[b]	*M. luteus*[c]	*B. subtilis*[d]	*E. coli*[e]	*P. aeruginosa*[f]
4a	8.0	>40.0	2.5	1.0	>40.0	>40.0
4b	>30.0	9.0	8.0	16.0	>40.0	>40.0
4c	**0.5**	6.0	3.0	1.0	>40.0	>40.0
4d	>30.0	5.0	>30.0	12.0	>40.0	>40.0
4e	NT	NT	NT	NT	NT	NT
4f	8.0	>30.0	>30.0	>30.0	>40.0	>40.0
4g	16.0	>30.0	>30.0	>30.0	>40.0	>40.0
4h	10.0	>30.0	10.0	>30.0	>40.0	>40.0
4i	10.0	>30.0	>30.0	>30.0	>40.0	>40.0
4j	>40.0	10.0	8.0	>40.0	>40.0	>40.0
4k	>40.0	>40.0	8.0	>40.0	>40.0	>40.0
4l	8.0	9.0	**0.5**	2.5	>40.0	>40.0
4m	NT	NT	NT	NT	NT	NT
4n	>40.0	>40.0	>40.0	9.0	>40.0	>40.0
5a	3.0	5.0	5.0	2.5	>40.0	>40.0
5b	**0.5**	2.0	1.5	1.5	>40.0	>40.0
5c	2.0	6.0	3.0	1.5	>40.0	>40.0
5d	1.5	5.0	1.5	3.0	>40.0	>40.0
LZ	1.5	0.5	1.0	0.5	–	–

The tests were performed in duplicate and repeated thrice; NT (Not Tested) LZ (Linezolid); AT-B (Amphotericin). Bold represents MIC values of the active compounds.
[a] *S. aureus* (*Staphylococcus aureus* MTCC 96).
[b] *S. MLS-16* (*Staphylococcus MLS-16* MTCC 2940).
[c] *M. luteus* (*Micrococcus luteus* MTCC 2470).
[d] *B. subtilis* (*Bacillus subtilis* MTCC 121).
[e] *E. coli* (*Escherichia coli* MTCC 739).
[f] *P. aeruginosa* (*Pseudomonas aeruginosa* MTCC 2453).

6.86 (d, 2H, J = 3.1 Hz, Ar–*H*), 6.75 (s, 1H, Ar–*H*), 6.24 (d, 1H, J = 3.2 Hz, pyr–*H*), 6.03 (d, 1H, J = 3.2 Hz, pyr–*H*), 2.11 (s, 3H, pyr–C*H*$_3$); ESIMS: m/z 316 $(M + H)^+$.

5.2.4. 2-(3-Chlorophenyl)-1-(2-fluorophenyl)-5-methylpyrrole (*9d*)

The compound **9d** was prepared according to the above-described method using 1-(3-chlorophenyl)-1,4-pentanedione (**8c**, 252 mg, 1.2 mmol) and 2-fluoroaniline (111 mg, 1.0 mmol) (yield 273 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.30 (s, 1H, Ar–*H*), 7.24 (dd, 1H, J = 8.3, 2.2 Hz, Ar–*H*), 7.12 (dd, 1H, J = 8.3, 2.2 Hz, Ar–*H*), 7.09 (d, 1H, J = 2.7 Hz, Ar–*H*), 7.02 (d, 1H, J = 8.8 Hz, Ar–*H*), 6.85 (dd, 1H, J = 8.8, 3.2 Hz, Ar–*H*), 6.40 (d, 1H, J = 3.2 Hz, Ar–*H*), 6.27 (d, 1H, J = 3.6 Hz, pyr–*H*), 6.07 (d, 1H, J = 3.6 Hz, pyr–*H*), 2.03 (s, 3H, pyr–C*H*$_3$); ESIMS: m/z 286 $(M + H)^+$.

5.2.5. 1-(4-Trifluoromethoxyphenyl)-2-methyl-5-(4-chloro-3-fluorolphenyl)-pyrrole (*9e*)

The compound **9e** was prepared according to the above-described method using 1-(4-chloro-3-fluorophenyl)-1,4-pentanedione (**8f**, 273 mg, 1.2 mmol) and 4-trifluoromethoxyaniline (177 mg, 1.0 mmol) (yield 349 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.23 (m, 2H, J = 9.0 Hz, Ar–*H*), 7.14–7.19 (m, 2H, Ar–*H*), 7.09–7.11 (m, 1H, J = 8.3 Hz, Ar–*H*), 6.76 (dd, 1H, J = 10.5, 2.2 Hz, Ar–*H*), 6.66 (d, 1H, J = 9.0 Hz, Ar–*H*), 6.33 (d, 1H, J = 3.7 Hz, pyr–*H*), 6.04 (d, 1H, J = 3.7 Hz, pyr–*H*), 2.12 (s, 3H, pyr–C*H*$_3$); ESIMS: m/z 352 $(M + H)^+$.

Table 5
Preliminary antibacterial activity of diarylpyrrole–triazolyloxazolidinones against Gram-positive bacteria (zone of inhibition in mm) at 20 μg/mL.

Entry	Compd	*S. aureus*[a]	*S. MLS − 16*[b]	*M. luteus*[c]	*B. subtilis*[d]
1	**4c**	39	40	36	24
2	**4l**	21	19	17	14
3	**5a**	20	18	19	14
4	**5b**	18	23	27	18
5	**5c**	16	15	18	12
6	LZ	28	18	20	20
7	AT-B	–	–	–	–

The tests were performed in duplicate and repeated thrice; LZ Linezolid (20 mg/mL); AT-B Amphotericin (20 mg/mL).
[a] *S. aureus* (*Staphylococcus aureus* MTCC 96).
[b] *S. MLS-16* (*Staphylococcus MLS-16* MTCC 2940).
[c] *M. luteus* (*Micrococcus luteus* MTCC 2470).
[d] *B. subtilis* (*Bacillus subtilis* MTCC 121).

5.2.6. 1-(3,4-Difluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1H-pyrrole (*9f*)

The compound **9f** was prepared according to the above-described method using 1-(2-methylphenyl)-1,4-pentanedione (**8e**, 261 mg, 1.2 mmol) and 2,4-difluoroaniline (129 mg, 1.0 mmol) (yield 293 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, 1H, J = 2.3 Hz, Ar–*H*), 7.31 (t, 2H, J = 3.0 Hz, Ar–*H*), 7.24 (t, 2H, J = 3.0 Hz, Ar–*H*), 7.18 (d, 1H, J = 2.3 Hz, Ar–*H*), 7.09 (s, 1H, Ar–*H*), 6.22 (d, 1H, J = 3.4 Hz, pyr–*H*), 5.96 (d, 1H, J = 3.4 Hz, pyr–*H*), 2.85–2.76 (m, 1H, –C*H*(CH$_3$)$_2$), 2.06 (s, 3H, pyr–C*H*$_3$), 1.6 (d, 6H, J = 6.9 Hz, –CH(C*H*$_3$)$_2$); ESIMS: m/z 312 $(M + H)^+$.

5.2.7. 1-(3,4-Fluorophenyl)-2-methyl-5-(2-methylphenyl)-pyrrole (*9g*)

The compound **9g** was prepared according to the above-described method using 1-(2-methylphenyl)-1,4-pentanedione (**8e**, 228 mg, 1.2 mmol) and 3,4-difluoroaniline (129 mg, 1.0 mmol) (yield 271 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15–7.13 (m, 2H, Ar–*H*), 7.10–7.01 (m, 3H, Ar–*H*), 6.87 (td, 2H, J = 7.2, 2.0 Hz, Ar–*H*), 6.35 (m, 1H, J = 3.4 Hz, pyr–*H*), 6.13 (d, 1H, J = 3.4 Hz, pyr–*H*), 2.16 (s, 3H, Ar–C*H*$_3$), 2.10 (s, 3H, pyr–C*H*$_3$); ESIMS: m/z 284 $(M + H)^+$.

5.2.8. 1-(4-Fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrole (*9h*)

The compound **9h** was prepared according to the above-described method using 1-(2-methylphenyl)-1,4-pentanedione (**8e**, 228 mg, 1.2 mmol) and 4-fluoroaniline (111 mg, 1.0 mmol) (yield 271 mg, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09–7.10 (m, 2H, Ar–*H*), 6.99–7.01 (m, 4H, Ar–*H*), 6.70 (td, 2H, J = 7.2, 2.0 Hz, Ar–*H*), 6.35 (m, 1H, J = 3.4 Hz, pyr–*H*), 6.13 (d, 1H, J = 3.4 Hz, pyr–*H*), 2.15 (s, 3H, Ar–C*H*$_3$), 2.10 (s, 3H, pyr–C*H*$_3$); ESIMS: m/z 266 $(M + H)^+$.

5.3. General procedure for the preparation of compounds *11a–h*

The compounds (**11a**–**h**) were prepared by means of the Mannich reaction as shown in Scheme 1, starting from a suitable pyrrole (**9a**–**h**) and (*R*)-5-(azidomethyl)-3-(3-fluoro-4-(piperazin-1-yl) phenyl)oxazolidin-2-one in acetonitrile and acetic acid, in the presence of formaldehyde. In detail, to a stirred solution of an appropriate pyrrole (0.6 mmol), in acetonitrile (5 mL), a mixture of (*R*)-5-(azidomethyl)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)oxazolidin-2-one (0.19 g, 0.6 mmol), formaldehyde (0.6 mmol) (40% in water), and 0.5 mL of acetic acid, was added drop wise at 0 °C. After the addition was complete, the mixture was stirred at room

Table 6
Docking scores for the compounds (**4a**–**c**, **4f**, **4i**, **4l**, **5a**, **5c** and **5d**).

Entry	Compound	Fitness score
1	**4a**	74.92
2	**4b**	61.45
3	**4c**	83.37
4	**4f**	72.66
5	**4i**	78.27
6	**4l**	70.04
7	**5a**	72.93
8	**5c**	64.27
9	**5d**	68.38

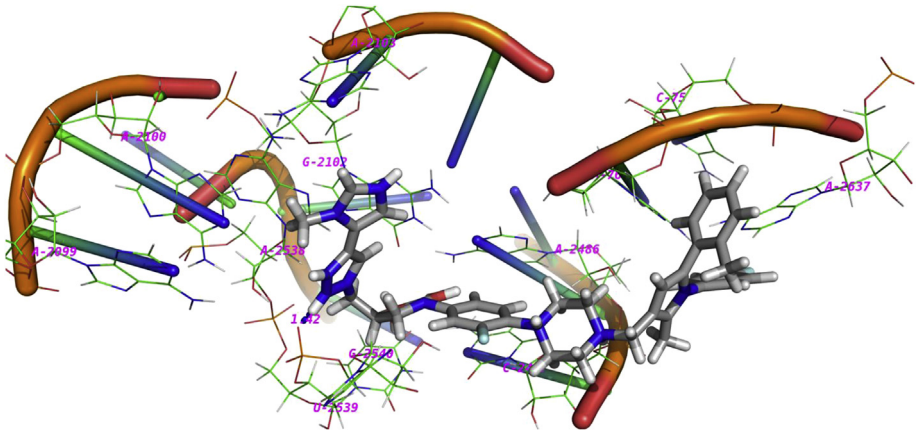


Fig. 2. Binding pose for **4i** in 50S unit of ribosome.

temperature for 6 h. The mixture was then treated with a solution of sodium hydroxide (20%, w/v) and extracted with chloroform. The organic extracts were combined, washed with water, and dried. After the removal of solvent, the residue was purified by column chromatography, using aluminum oxide and chloroform. The eluates were combined after TLC control, and the solvent was removed to give **11a**–**h** as solids in satisfactory yield. Recrystallization from diethyl ether gave the required products.

*5.3.1. (5R)-5-(Azidomethyl)-3-(4-(4-((1-(2-bromo-5-fluorophenyl)-5-(2,4-difluorophenyl)-2-methyl-1H-pyrrol-3-yl) methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11a**)*

The compound **11a** was prepared according to the above-described method using **9a** (0.220 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.334 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.40 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–*H*), 7.39 (d, 1H, J = 2.9 Hz, Ar–*H*), 7.34 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.22 (d, 1H, J = 2.9 Hz, Ar–*H*), 7.04 (d, 1H, J = 9.0 Hz, oxa–Ar–*H*), 7.02 (s, 1H, Ar–*H*), 6.89 (t, 1H, J = 8.9 Hz, oxa–Ar–*H*), 6.85 (s, 1H, Ar–*H*), 6.21 (d, 1H, J = 3.4 Hz, pyr–*H*), 4.78–4.70 (m, 1H, oxa–C*H*–), 4.00 (dd, 1H, J = 6.1 Hz, 9.0 Hz, oxa–CH*H*–), 3.73 (dd, 1H, J = 9.1, 6.2 Hz, oxa–C*H*H–), 3.57–3.48 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.12–3.07 (t, 4H, piperazine–*H*), 2.74–2.63 (t, 4H, piperazine–*H*), 2.02 (s, 3H, pyr–CH_3); ESIMS: m/z 698 $(M)^+$.

*5.3.2. (5R)-5-(Azidomethyl)-3-(4-(4-((5-(2,4-difluorophenyl)-1-(4-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11b**)*

The compound **11b** was prepared according to the above-described method using **9b** (0.172 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.278 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (dd, 1H, J = 14.0, 1.7 Hz, oxa–Ar–*H*), 7.10–7.04 (m, 3H, oxa–Ar–*H*, Ar–*H*), 7.00 (d, 2H, J = 6.5 Hz, Ar–*H*), 6.90 (t, 1H, J = 9.0 Hz, oxa–Ar–*H*), 6.73–6.63 (m, 3H, Ar–*H*), 6.33 (s, 1H, pyr–*H*), 5.13–5.05 (m, 1H, oxa–C*H*–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.85 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.17 (s, 3H, pyr–CH_3); ESIMS: m/z 620 $(M + H)^+$.

*5.3.3. (R)-5-(Azidomethyl)-3-(4-(4-((1-(3,4-dichlorophenyl)-2-methyl-5-p-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11c**)*

The compound **11c** was prepared according to the above-described method using **9c** (0.189 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.330 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–*H*), 7.40 (d, 2H, J = 6.7 Hz, Ar–*H*), 7.35–7.27 (m, 3H, Ar–*H*), 7.02 (t, 1H, J = 1.9 Hz, oxa–Ar–*H*), 6.97–6.84 (m, 2H, Ar–*H* and 1H, oxa–Ar–*H*), 6.30 (s, 1H, pyr–*H*), 5.08–5.04 (m, 1H, oxa–C*H*–), 4.73–4.08 (m, 2H, oxa–CH_2–), 4.16 (dd, 1H, J = 6.8, 2.9 Hz, oxa–CH*H*–), 3.93 (dd, 1H, J = 6.8, 2.9 Hz, oxa–C*H*H–), 3.65 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.86–2.82 (t, 4H, piperazine–*H*), 2.27 (s, 3H, Ar–CH_3), 2.11 (s, 3H, pyr–CH_3); ESIMS: m/z 649 $(M)^+$.

*5.3.4. (5R)-5-(Azidomethyl)-3-(4-(4-((5-(3-chlorophenyl)-1-(2-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11d**)*

The compound **11d** was prepared according to the above-described method using **9d** (0.171 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.330 g, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, 1H, J = 2.6 Hz, Ar–*H*), 7.41 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–*H*), 7.21 (td, 1H, J = 8.8, 1.7 Hz, Ar–*H*), 7.17 (d, 2H, J = 5.2 Hz, Ar–*H*), 7.12–7.09 (m, 2H, Ar–*H*), 7.07 (s, 1H, Ar–*H*), 7.02 (dd, 1H, J = 8.8, 2.2 Hz, oxa–Ar–*H*), 6.95 (d, 1H, J = 9.0 Hz, Ar–*H*), 6.90 (dt, 1H, J = 6.7, 1.8 Hz, oxa–Ar–*H*), 6.39 (s, 1H, pyr–*H*), 4.77–4.68 (m, 1H, oxa–C*H*–), 3.97 (dd, 1H, J = 9.0, 6.1 Hz, oxa–CH*H*–), 3.87 (dd, 1H, J = 9.1, 6.2 Hz, oxa–C*H*H–), 3.64–3.59 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.15–3.07 (t, 4H, piperazine–*H*), 2.74–2.63 (t, 4H, piperazine–*H*), 1.99 (s, 3H, pyr–CH_3); ESIMS: m/z 619 $(M + H)^+$.

*5.3.5. (R)-5-(Azidomethyl)-3-(4-(4-((5-(4-chloro-3-fluorophenyl)-2-methyl-1-(4-(trifluoromethoxy)phenyl)-1H-pyrrol-3-yl)methyl) piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11e**)*

The compound **11e** was prepared according to the above-described method using **9e** (0.214 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.336 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (dd, 1H, J = 12.0, 1.7 Hz, oxa–Ar–*H*), 7.26–7.23 (m, 2H, Ar–*H*), 7.14–7.19 (m, 2H, Ar–*H*), 7.11–7.06 (m, 2H, oxa–Ar–*H*, Ar–*H*), 6.90 (t, 1H, J = 9.0 Hz, oxa–Ar–*H*), 6.73–6.63 (m, 2H, Ar–*H*), 6.33 (s, 1H, pyr–*H*), 5.13–5.05 (m, 1H, oxa–C*H*–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.85 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.17 (s, 3H, pyr–CH_3); ESIMS: m/z 703 $(M + H)^+$.

*5.3.6. (R)-5-(Azidomethyl)-3-(4-(4-((1-(2,4-difluorophenyl)-5-(4-isopropylphenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11f**)*

The compound **11f** was prepared according to the above-described method using **9f** (0.187 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.320 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, 1H, J = 2.6 Hz, Ar–*H*), 7.41 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–*H*),

7.21 (td, 1H, J = 8.8, 1.7 Hz, Ar–H), 7.17 (d, 2H, J = 5.2 Hz, Ar–H), 7.12–7.09 (m, 2H, Ar–H), 7.07 (s, 1H, Ar–H), 7.02 (dd, 1H, J = 8.8, 2.2 Hz, oxa–Ar–H), 6.95 (d, 1H, J = 9.0 Hz, oxa–Ar–H), 6.39 (s, 1H, pyr–H), 4.77–4.68 (m, 1H, oxa–CH–), 3.97 (dd, 1H, J = 6.1, 9.0 Hz, oxa–CHH–), 3.87 (dd, 1H, J = 9.1, 6.2 Hz, oxa–CHH–), 3.64–3.59 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.15–3.07 (t, 4H, piperazine–H), 2.74–2.63 (t, 4H, piperazine–H), 1.99 (s, 3H, pyr–CH_3); ESIMS: m/z 644 $(M + H)^+$.

*5.3.7. (5R)-5-(Azidomethyl)-3-(3-fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)phenyl) oxazolidin-2-one (**11g**)*

The compound **11g** was prepared according to the above-described method using **9g** (0.170 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.304 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (dd, 1H, J = 12.0, 1.7 Hz, oxa–Ar–H), 7.06 (d, 1H, J = 9.0 Hz, oxa–Ar–H), 6.99 (d, 2H, Ar–H), 6.91 (t, 1H, J = 9.0 Hz, oxa–Ar–H), 6.83 (s, 1H, Ar–H), 6.85–6.81 (m, 3H, Ar–H), 6.73–6.63 (m, 2H, Ar–H), 6.33 (s, 1H, pyr–H), 5.13–5.05 (m, 1H, oxa–CH–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CHH–), 3.84 (dd, 1H, J = 6.4, 3.0 Hz, oxa–CHH–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–H), 2.87–2.85 (t, 4H, piperazine–H), 2.17 (s, 3H, pyr–CH_3); ESIMS: m/z 598 $(M + H)^+$.

*5.3.8. (5R)-5-(Azidomethyl)-3-(4-(4-((1-(3,4-difluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**11h**)*

The compound **11h** was prepared according to the above-described method using **9h** (0.159 g, 0.6 mmol) and **10** (0.192 g, 0.6 mmol) (yield 0.306 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (dd, 1H, J = 14.5, 3.0 Hz, oxa–Ar–H), 7.06 (s, 1H, Ar–H), 7.01–6.98 (m, 4H, Ar–H and 1H, oxa–Ar–H), 6.95–6.92 (m, 2H, Ar–H and 1H, oxa–Ar–H), 6.20 (s, 1H, pyr–H), 4.78–4.72 (m, 1H, oxa–CH–), 3.99 (dd, 1H, J = 9.0, 6.1 Hz, oxa–CHH–), 3.76–3.73 (m, 3H, oxa–CH_2–, oxa–CHH–), 3.67–3.59 (t, 4H, piperazine–H), 3.47 (s, 2H, pyr–CH_2), 3.25 (t, 4H, piperazine–H), 2.15 (s, 3H, NHCOCH_3), 2.12 (s, 3H, Ar–CH_3), 2.01 (s, 3H, pyr–CH_3); ESIMS: m/z 616 $(M + H)^+$.

5.4. General procedure for the preparation of compounds ***12a–d***

The compounds (**12a–d**) were prepared by reduction of azide group of compounds **11a**, **11d**, **11f** and **11h** in the presence of Pd/C under H_2 gas in ethanol. In detail, to a stirred solution of appropriate azido compound (0.2 mmol) in ethanol (5 mL), slowly Pd/C (1 mmol) was added. After the addition was complete, the mixture was stirred at room temperature for 3 h under hydrogen gas. After completion of reaction as indicated by TLC, The reaction mixture was filtered by using celite and from filtrate solvent was removed under reduced pressure and the product was recrystallized from ethanol.

*5.4.1. (5S)-5-(Aminomethyl)-3-(4-(4-((1-(2-bromo-5-fluorophenyl)-5-(2,4-difluorophenyl)-2-methyl-1H-pyrrol-3-yl) methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**12a**)*

The compound **12a** was prepared according to the above-described method using **11a** (0.139 g, 0.2 mmol) (yield 0.127 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, 1H, J = 2.2 Hz, Ar–H), 7.40 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–H), 7.39 (d, 1H, J = 2.9 Hz, Ar–H), 7.34 (d, 1H, J = 2.2 Hz, Ar–H), 7.22 (d, 1H, J = 2.9 Hz, Ar–H), 7.04 (d, 1H, J = 9.0 Hz, oxa–Ar–H), 7.02 (s, 1H, Ar–H), 6.89 (t, 1H, J = 8.9 Hz, oxa–Ar–H), 6.85 (s, 1H, Ar–H), 6.21 (d, 1H, J = 3.4 Hz, pyr–H), 5.97 (d, 1H, J = 3.4 Hz, pyr–H), 4.78–4.70 (m, 1H, oxa–CH–), 4.00 (dd, 1H, J = 6.1 Hz, 9.0 Hz, oxa–CHH–), 3.74 (dd, 1H, J = 6.2 Hz, 9.1 Hz, oxa–CHH–), 3.57–3.48 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.09 (t, 4H, pip–H), 2.74–2.63 (t, 4H, pip–H), 2.02 (s, 3H, pyr–CH_3); ESIMS: m/z 672 $(M)^+$, 674 $(M + 2)^+$.

*5.4.2. (5S)-5-(Aminomethyl)-3-(4-(4-((5-(3-chlorophenyl)-1-(2-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**12b**)*

The compound **12b** was prepared according to the above-described method using **11d** (0.123 g, 0.2 mmol) (yield 0.110 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, 1H, J = 2.6 Hz, Ar–H), 7.41 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–H), 7.21 (td, 1H, J = 8.8, 1.7 Hz, Ar–H), 7.17 (d, 2H, J = 5.2 Hz, Ar–H), 7.12–7.09 (m, 2H, Ar–H), 7.07 (s, 1H, Ar–H), 7.02 (dd, 1H, J = 8.8, 2.2 Hz, oxa–Ar–H), 6.95 (d, 1H, J = 9.0 Hz, Ar–H), 6.90 (dt, 1H, J = 6.7, 1.8 Hz, oxa–Ar–H), 6.62 (t, 2H, J = 5.2, –NH_2), 6.39 (s, 1H, pyr–H), 4.77–4.68 (m, 1H, oxa–CH–), 3.97 (dd, 1H, J = 6.1 Hz, 9.0 Hz, oxa–CHH–), 3.87 (dd, 1H, J = 9.1, 6.2 Hz, oxa–CHH–), 3.64–3.59 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.15–3.07 (t, 4H, piperazine–H), 2.74–2.63 (t, 4H, piperazine–H), 1.99 (s, 3H, pyr–CH_3); ESIMS: m/z 593 $(M + H)^+$.

*5.4.3. (5S)-5-(Aminomethyl)-3-(4-(4-((1-(2,4-difluorophenyl)-5-(4-isopropylphenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)oxazolidin-2-one (**12c**)*

The compound **12c** was prepared according to the above-described method using **11f** (0.128 g, 0.6 mmol) (yield 0.112 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–H), 7.21 (td, 1H, J = 8.8, 1.7 Hz, Ar–H), 7.17 (d, 2H, J = 5.2 Hz, Ar–H), 7.12–7.09 (m, 2H, Ar–H), 7.07 (s, 1H, Ar–H), 7.02 (dd, 1H, J = 8.8, 2.2 Hz, oxa–Ar–H), 6.97–6.94 (d, 1H, J = 9.0 Hz, Ar–H), 6.90 (dt, 1H, J = 6.7, 1.8 Hz, oxa–Ar–H), 6.39 (s, 1H, pyr–H), 4.77–4.68 (m, 1H, oxa–CH–), 3.97 (dd, 1H, J = 6.1, 9.0 Hz, oxa–CHH–), 3.87 (dd, 1H, J = 9.1, 6.2 Hz, oxa–CHH–), 3.64–3.59 (m, 2H, oxa–CH_2–), 3.47 (s, 2H, pyr–CH_2), 3.15–3.07 (t, 4H, piperazine–H), 2.74–2.63 (t, 4H, piperazine–H), 1.99 (s, 3H, pyr–CH_3); ESIMS: m/z 618 $(M + H)^+$.

*5.4.4. (5S)-5-(Aminomethyl)-3-(3-fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)phenyl)oxazolidin-2-one (**12d**)*

The compound **12d** was prepared according to the above-described method using **11h** (0.123 g, 0.6 mmol) (yield 0.101 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (dd, 1H, J = 14.5, 3.0 Hz, oxa–Ar–H), 7.06 (s, 2H, Ar–H), 7.01–6.98 (m, 4H, Ar–H and 1H, oxa–Ar–H), 6.95–6.92 (m, 2H, Ar–H and 1H, oxa–Ar–H), 6.43–6.32 (bs, 2H, –NH_2), 6.20 (s, 1H, Pyr–H), 4.78–4.72 (m, 1H, oxa–CH–), 4.01–3.97 (dd, 1H, J = 6.1 Hz, 9.0 Hz, oxa–CHH–), 3.76–3.73 (m, 3H, oxa–CH_2–, oxa–CHH–), 3.67–3.59 (t, 4H, piperazine–H), 3.47 (s, 2H, pyr–CH_2), 3.25 (t, 4H, piperazine–H), 2.12 (s, 3H, Ar–CH_3), 2.01 (s, 3H, pyr–CH_3); ESIMS: m/z 572 $(M + H)^+$.

5.5. General procedure for the preparation of compounds ***4a–n***

The compounds (**4a–n**) were prepared from azido compounds (**11a–h**) and aryl/heteroaryl acetylenes by employing CuAAC reaction. In detail, to a stirred solution of appropriate azido compound (0.15 mmol) in 3:1 of t-BuOH and H_2O (5 mL), $CuSO_4$ (0.10 mmol) was added. Then appropriate aryl/heteroacetylene (0.15 mmol) was added to the reaction mixture followed by addition of catalytic amount of sodium ascorbate. The mixture was stirred at room temperature for 4 h. After completion of reaction as indicated by TLC, water (5 mL) was added to reaction mixture and the product was extracted with dichloromethane (2 × 5 mL). The organic layers were combined, solvent was removed under reduced pressure and the product was purified by column chromatography by using chloroform methanol (10:1) system to give the product.

*5.5.1. (R)-3-(4-(4-((1-(3,4-Dichlorophenyl)-2-methyl-5-p-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4a**)*

The compound **4a** was prepared according to the above-described method using **11c** (0.097 g, 0.15 mmol) (yield 0.090 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.57 (d, 1H, J = 6.0 Hz, pyridine–*H*), 8.35 (s, 1H, triazole–*H*), 8.10 (d, 1H, J = 7.9 Hz, pyridine–*H*), 7.77 (tb, 1H, J = 7.7, 1.7 Hz, pyridine–*H*), 7.71–7.50 (m, 1H, pyridine–*H*), 7.42 (d, 1H, J = 14.0 Hz, oxa–Ar–*H*), 7.37–7.30 (m, 2H, Ar–*H*), 7.22 (dd, 1H, J = 7.3, 2.4 Hz, Ar–*H*), 7.03 (d, 1H, J = 8.1 Hz, oxa–Ar–*H*), 7.00–6.95 (m, 3H, oxa–Ar–*H*, Ar–*H*), 6.93 (s, 1H, Ar–*H*), 6.88 (d, 1H, J = 3.7 Hz, Ar–*H*), 6.31 (s, 1H, pyr–*H*), 5.12–5.04 (m, 1H, oxa–C*H*–), 4.13 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.94 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.70–3.63 (m, 2H, oxa–CH_2–), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.27 (s, 3H, pyr–CH_3), 2.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.2, 150.1, 149.4, 148.9, 136.9, 135.5, 132.9, 131.1, 130.8, 130.7, 130.4, 130.1, 129.4, 129.0, 128.7, 127.8, 127.7, 126.6, 123.5, 123.1, 120.2, 119.4, 114.0, 111.1, 107.7, 107.4, 70.3, 53.5, 52.2, 51.5, 48.7, 32.8, 21.3, 10.9; ESIMS: m/z 751 $(M)^+$; HRMS: (ESI m/z) for $C_{40}H_{38}Cl_2FN_8O_2$ calcd: 751.2478, found: 751.2468 $(M)^+$.

*5.5.2. (R)-3-(4-(4-((5-(4-Chloro-3-fluorophenyl)-2-methyl-1-(4-(trifluoromethoxy)phenyl)-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4b**)*

The compound **4b** was prepared according to the above-described method using **11e** (0.105 g, 0.15 mmol) (yield 0.090 g, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59 (d, 1H, J = 4.3 Hz, pyridine–*H*), 8.36 (s, 1H, triazole–*H*), 8.12 (d, 1H, J = 7.7 Hz, pyridine–*H*), 7.79 (t, 1H, J = 7.9 Hz, pyridine–*H*), 7.35 (dd, 1H, J = 12.0 Hz, 1.7 Hz, oxa–Ar–*H*), 7.26–7.23 (m, 3H, J = 9.0 Hz, pyridine–*H*, Ar–*H*), 7.14–7.19 (m, 2H, Ar–*H*), 7.11–7.06 (m, 2H, oxa–Ar–*H*, Ar–*H*), 6.90 (t, 1H, J = 9.0 Hz, oxa–Ar–*H*), 6.87–6.85 (m, 2H, Ar–*H*), 6.32 (s, 1H, pyr–*H*), 5.13–5.05 (m, 1H, oxa–C*H*–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.85 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.27 (s, 3H, pyr–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.4, 153.2, 150.1, 149.4, 148.9, 136.9, 135.5, 132.9, 131.1, 130.8, 130.6, 130.4, 130.0, 129.6, 129.0, 128.7, 127.8, 127.7, 126.5, 125.5, 123.5, 123.2, 120.2, 119.4, 114.0, 111.1, 107.7, 107.4, 70.3, 53.1, 52.0, 51.5, 48.7, 38.6, 11.2; ESIMS: m/z 805 $(M + H)^+$; HRMS: (ESI m/z) for $C_{40}H_{35}ClF_5N_8O_3$ calcd: 805.2441, found: 805.2449 $(M + H)^+$.

*5.5.3. (5R)-3-(4-(4-((5-(2,4-Difluorophenyl)-1-(4-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4c**)*

The compound **4c** was prepared according to the above-described method using **11b** (0.092 g, 0.15 mmol) (yield 0.085 g, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59 (d, 1H, J = 4.3 Hz, pyridine–*H*), 8.38 (s, 1H, triazole–*H*), 8.12 (d, 1H, J = 7.7 Hz, pyridine–*H*), 7.79 (t, 1H, J = 7.9 Hz, pyridine–*H*), 7.35 (dd, 1H, J = 12.0, 1.7 Hz, oxa–Ar–*H*), 7.10–7.04 (m, 4H, pyridine–*H*, oxa–Ar–*H*, Ar–*H*), 7.00 (d, 2H, J = 6.5 Hz, Ar–*H*), 6.90 (t, 1H, J = 9.0 Hz, oxa–Ar–*H*), 6.73–6.63 (m, 3H, Ar–*H*), 6.33 (s, 1H, pyr–*H*), 5.13–5.05 (m, 1H, oxa–C*H*–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.85 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.17 (s, 3H, pyr–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 163.1, 160.2, 156.8, 153.2, 150.1, 149.4, 148.9, 136.9, 132.9, 130.8, 130.6, 130.4, 130.0, 129.6, 129.0, 128.7, 127.8, 126.5, 125.5, 123.5, 123.2, 120.2, 119.4, 114.0, 111.1, 107.7, 107.4, 70.4, 53.2, 52.0, 51.5, 48.7, 38.6, 11.1; ESIMS: m/z 723 $(M + H)^+$; HRMS: (ESI m/z) for $C_{39}H_{35}F_4N_8O_2$ calcd: 723.2819, found: 723.2843 $(M + H)^+$.

*5.5.4. (5R)-3-(4-(4-((1-(3,4-Difluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4d**)*

The compound **4d** was prepared according to the above-described method using **11g** (0.123 g, 0.15 mmol) (yield 0.091 g, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59–8.58 (d, 1H, J = 4.3 Hz, pyridine–*H*), 8.35 (s, 1H, triazole–*H*), 8.11 (d, 1H, J = 7.7 Hz, pyridine–*H*), 7.79 (t, 1H, J = 7.9 Hz, pyridine–*H*), 7.34 (dd, 1H, J = 12.0, 1.7 Hz, oxa–Ar–*H*), 7.10–7.04 (m, 2H, oxa–Ar–*H* and pyridine–*H*), 7.00 (d, 2H, Ar–*H*), 6.91 (t, 1H, J = 9.0 Hz, oxa–Ar–*H*), 6.83 (s, 1H, Ar–*H*), 6.85–6.81 (m, 3H, Ar–*H*), 6.73–6.63 (m, 2H, Ar–*H*), 6.33 (s, 1H, pyr–*H*), 5.13–5.05 (m, 1H, oxa–C*H*–), 4.82–4.79 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.88–3.83 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.69 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.17 (s, 3H, pyr–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 168.0, 157.9, 156.2, 155.2, 151.3, 139.9, 136.1, 136.0, 130.4, 129.8, 128.6, 123.7, 122.6, 122.3, 122.2, 122.1, 120.3, 119.1, 119.0, 118.5, 118.0, 112.9, 110.4, 107.6, 107.5, 70.6, 54.5, 53.9, 49.5, 46.2, 24.0, 11.9; ESIMS: m/z 719 $(M + H)^+$; HRMS: (ESI m/z) for $C_{40}H_{38}F_3N_8O_2$ calcd: 719.3069, found: 719.3082 $(M + H)^+$.

*5.5.5. (5R)-3-(4-(4-((1-(2-Bromo-5-fluorophenynel)-5-(2,4-difluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4e**)*

The compound **4e** was prepared according to the above-described method using **11a** (0.104 g, 0.15 mmol) (yield 0.092 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.60–8.58 (d, 1H, J = 4.3 Hz, pyridine–*H*), 8.38 (s, 1H, triazole–*H*), 8.12 (d, 1H, J = 7.7 Hz, pyridine–*H*), 7.70 (t, 1H, J = 7.9 Hz, pyridine–*H*), 7.49 (d, 1H, J = 2.2 Hz, Ar–*H*), 7.40 (dd, 1H, J = 14.6, 2.4 Hz, oxa–Ar–*H*), 7.10–7.04 (m, 2H, pyridine–*H*, Ar–*H*), 7.40–7.35 (m, 1H, Ar–*H*), 7.23 (d, 1H, J = 2.9 Hz, Ar–*H*), 7.04 (d, 1H, J = 9.0 Hz, oxa–Ar–*H*), 7.02 (s, 1H, Ar–*H*), 6.89 (t, 1H, J = 8.9 Hz, oxa–Ar–*H*), 6.85 (s, 1H, Ar–*H*), 6.29 (d, 1H, J = 3.4 Hz, pyr–*H*), 5.13–5.07 (m, 1H, oxa–C*H*–), 4.82–4.75 (m, 2H, oxa–CH_2–), 4.15 (dd, 1H, J = 6.2, 3.1 Hz, oxa–CH*H*–), 3.89 (dd, 1H, J = 6.4, 3.0 Hz, oxa–C*H*H–), 3.66 (s, 2H, pyr–CH_2), 3.18–3.16 (t, 4H, piperazine–*H*), 2.87–2.85 (t, 4H, piperazine–*H*), 2.12 (s, 3H, pyr–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.4, 160.7, 156.8, 153.8, 153.3, 148.4, 148.2, 138.5, 136.2, 132.4, 131.7, 130.8, 130.6, 130.2, 130.1, 129.2, 129.0, 128.8, 128.4, 127.9, 127.7, 126.0, 125.7, 121.0, 119.0, 114.1, 113.8, 111.1, 107.7, 107.4, 70.4, 53.8, 52.1, 51.9, 49.5, 47.3, 38.7, 10.9; ESIMS: m/z 801 $(M)^+$; HRMS: (ESI m/z) for $C_{39}H_{34}BrF_4N_8O_2$ calcd: 801.1924, found: 801.1969 $(M)^+$.

*5.5.6. (5R)-3-(4-(4-((1-(2,4-Difluorophenyl)-5-(4-isopropylphenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(1-methyl-1H-imidazol-5-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4f**)*

The compound **4f** was prepared according to the above-described method using **11f** (0.096 g, 0.15 mmol) (yield 0.084 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (s, 1H, triazole–*H*), 7.53–7.50 (m, 1H, imidazole–*H*), 7.32–7.27 (d, 1H, J = 2.9 Hz, oxa–Ar–*H*), 7.25 (s, 1H, imidazole–*H*), 7.06 (d, 2H, J = 1.9 Hz, Ar–*H*), 7.05–6.91 (m, 4H, Ar–*H*, oxa–Ar–*H*), 6.96 (d, 1H, J = 1.9 Hz, Ar–*H*), 6.94–6.91 (t, 2H, J = 8.7 Hz, oxa–Ar–*H*), 6.89–6.87 (d, 1H, J = 9.68 Hz), 6.35 (s, 1H, pyr–*H*), 5.08–5.04 (m, 1H, oxa–C*H*–), 4.73–4.83 (m, 2H, oxa–CH_2–), 4.16–4.15 (dd, 1H, J = 6.7, 2.9 Hz, oxa–CH*H*–), 3.95–3.92 (dd, 1H, J = 2.9 Hz, 6.78 Hz, oxa–C*H*H–), 3.85 (s, 3H, N–CH_3), 3.58 (s, 2H, pyr–CH_2), 3.13 (t, 4H, piperazine–*H*), 2.85–2.78 (m, 1H, CH_3–C*H*–CH_3), 2.76 (t, 4H, piperazine–*H*), 2.05 (s, 3H, pyr–CH_3), 1.19–1.17 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.1, 160.2, 153.6, 153.3, 139.5, 139.0, 137.1, 136.9, 134.7, 131.9, 138.8, 129.9, 129.6, 129.5, 129.0, 125.7, 122.3, 119.0, 115.8, 115.4,

114.2, 112.6, 110.9, 110.7, 107.7, 107.4, 103.8, 103.4, 70.2, 54.2, 52.4, 52.3, 50.2, 47.4, 33.3, 31.3, 29.6, 11.1; ESIMS: *m/z* 750 $(M + H)^+$; HRMS: (ESI *m/z*) for $C_{41}H_{43}F_3N_9O_2$ calcd: 750.3491, found: 750.3458 $(M + H)^+$.

*5.5.7. (5R)-3-(4-(4-((5-(2,4-Difluorophenyl)-1-(4-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(1-methyl-1H-imidazol-5-yl)-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4g**)*

The compound **4g** was prepared according to the above-described method using **11b** (0.092 g, 0.6 mmol) (yield 0.078 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (s, 1H, triazole−*H*), 7.53−7.50 (m, 1H, imidazole−*H*), 7.32−7.27 (d, 1H, *J* = 2.9 Hz, oxa−Ar−*H*), 7.25 (s, 1H, imidazole−*H*), 7.10−7.04 (m, 4H, pyridine−*H*, oxa−Ar−*H*, Ar−*H*), 7.00 (d, 2H, *J* = 6.5 Hz, Ar−*H*), 6.90 (t, 1H, *J* = 9.0 Hz, oxa−Ar−*H*), 6.73−6.63 (m, 3H, Ar−*H*), 6.21 (s, 1H, pyr−*H*), 5.13−5.05 (m, 1H, oxa−C*H*−), 4.82−4.79 (m, 2H, oxa−CH_2−), 4.10−4.08 (dd, 1H, *J* = 6.2, 3.1 Hz, oxa−CH*H*−), 3.87 (m, 1H, oxa−C*H*−), 3.85 (s, 3H, N−CH_3), 3.69 (s, 2H, pyr−CH_2), 3.18−3.16 (t, 4H, piperazine−*H*), 2.87−2.85 (t, 4H, piperazine−*H*), 2.17 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 163.1, 160.2, 156.8, 153.6, 153.3, 148.4, 138.9, 136.1, 134.7, 132.1, 131.8, 130.8, 128.9, 128.5, 125.7, 122.3, 119.0, 115.8, 114.2, 112.6, 111.1, 110.6, 107.9, 107.7, 102.9, 103.5, 70.2, 54.2, 52.1, 51.9, 47.4, 30.2, 29.6, 11.1; ESIMS: *m/z* 726 $(M + H)^+$; HRMS: (ESI *m/z*) for $C_{38}H_{36}F_4N_9O_2$ calcd: 726.2928, found: 726.2958 $(M + H)^+$.

*5.5.8. (5R)-3-(4-(4-((1-(3,4-Difluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-(1-methyl-1H-imidazol-5-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4h**)*

The compound **4h** was prepared according to the above-described method using **11g** (0.089 g, 0.15 mmol) (yield 0.080 g, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (s, 1H, triazole−*H*), 7.53−7.50 (m, 1H, imidazole−*H*), 7.30 (d, 1H, *J* = 2.9 Hz, oxa−Ar−*H*), 7.25 (s, 1H, imidazole−*H*), 7.10−7.04 (m, 2H, oxa−Ar−*H*, Ar−*H*), 7.00 (d, 2H, Ar−*H*), 6.91 (t, 1H, *J* = 9.0 Hz, oxa−Ar−*H*), 6.83 (s, 1H, Ar−*H*), 6.85−6.81 (m, 2H, Ar−*H*), 6.73−6.63 (d, 1H, Ar−*H*), 6.33 (s, 1H, pyr−*H*), 5.13−5.05 (m, 1H, oxa−C*H*−), 4.82−4.79 (m, 2H, oxa−CH_2−), 4.15 (dd, 1H, *J* = 6.2, 3.1 Hz, oxa−CH*H*−), 3.87 (dd, 1H, *J* = 6.4, 3.0 Hz, oxa−C*H*H−), 3.85 (s, 3H, imidazole−N−CH_3), 3.51 (s, 2H, pyr−CH_2), 3.18−3.16 (t, 4H, piperazine−*H*), 2.87−2.85 (t, 4H, piperazine−*H*), 2.13 (s, 3H, Ar−CH_3), 2.12 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7, 160.7, 156.9, 153.2, 146.6, 139.6, 139.1, 137.2, 132.1, 131.4, 129.8, 129.6, 129.5, 127.1, 125.0, 122.3, 122.1, 119.1, 115.5, 115.2, 114.1, 113.9, 111.5, 111.3, 107.8, 107.4, 70.2, 54.2, 52.3, 50.1, 47.4, 33.4, 29.3, 20.5, 11.3; ESIMS: *m/z* 722 $(M + H)^+$; HRMS: (ESI *m/z*) for $C_{39}H_{39}F_3N_9O_2$ calcd: 722.3178, found: 722.3178 $(M + H)^+$.

*5.5.9. (5R)-3-(3-Fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)phenyl)-5-((4-(1-methyl-1H-imidazol-5-yl)-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4i**)*

The compound **4i** was prepared according to the above-described method using **11h** (0.092 g, 0.15 mmol) (yield 0.074 g, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (s, 1H, triazole−*H*), 7.48 (s, 1H, imidazole−*H*), 7.28−7.24 (dd, 1H, *J* = 14.6, 2.4 Hz, oxa−Ar−*H*), 7.25 (s, 1H, imidazole−*H*), 7.06 (d, 2H, *J* = 1.9 Hz, Ar−*H*), 7.06−6.91 (m, 2H, Ar−*H* and 2H, oxa−Ar−*H*), 6.96 (d, 1H, *J* = 1.9 Hz), 6.94−6.91 (t, 2H, *J* = 8.7 Hz), 6.89−6.87 (d, 1H, *J* = 9.6 Hz, oxa−Ar−*H*), 6.15 (s, 1H, pyr−*H*), 5.08−5.04 (m, 1H, oxa−C*H*−), 4.73−4.08 (m, 2H, oxa−CH_2−), 4.17−4.14 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−CH*H*−), 3.93 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−C*H*H−), 3.87 (s, 3H, imidazole−N−CH_3), 3.53 (s, 2H, pyr−CH_2), 3.10 (t, 4H, piperazine−*H*), 2.71 (t, 4H, piperazine−*H*), 2.12 (s, 3H, Ar−CH_3), 2.11 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.7, 156.9, 153.2, 139.6, 139.1, 137.2, 132.1, 131.4, 129.9, 129.7, 129.5, 127.2, 125.1, 122.4, 122.1, 119.1, 115.6, 115.2, 114.2, 113.9, 111.5, 111.3, 107.8, 107.3, 70.2, 54.2, 52.3, 50.2, 47.4, 33.4, 29.4, 20.4, 11.2; ESIMS: *m/z* 704 $(M + H)^+$; HRMS: (ESI *m/z*) for $C_{39}H_{40}F_2N_9O_2$ calcd: 704.3273, found: 704.3293 $(M + H)^+$.

*5.5.10. (5R)-3-(4-(4-((5-(3-Chlorophenyl)-1-(2-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)-piperazin-1-yl)-3-fluorophenyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4j**)*

The compound **4j** was prepared according to the above-described method using **11d** (0.092 g, 0.15 mmol) (yield 0.082 g, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H, triazole−*H*), 7.61 (dd, 1H, *J* = 2.6 Hz, Ar−*H*), 7.33−7.27 (m, 1H, oxa−Ar−*H* and 1H, Ar−*H*), 7.17 (d, 2H, *J* = 5.2 Hz, Ar−*H*), 7.08−7.05 (m, 2H, Ar−*H*), 7.01−6.97 (m, 2H, Ar−*H* and 2H, oxa−Ar−*H*), 6.94 (d, 2H, *J* = 9.0 Hz, Ar−*H*), 6.91−6.88 (m, 3H, Ar−*H*), 6.15 (s, 1H, pyr−*H*), 5.08−5.04 (m, 1H, oxa−C*H*−), 4.84−4.73 (m, 2H, oxa−CH_2−), 4.17−4.14 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−CH*H*−), 3.90 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−C*H*H−), 3.56 (s, 2H, pyr−CH_2), 3.11 (t, 4H, piperazine−*H*), 2.73 (t, 4H, piperazine−*H*), 2.17 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 160.5, 153.3, 148.5, 146.8, 138.5, 136.1, 132.2, 130.7, 130.2, 130.1, 129.1, 128.9, 128.8, 128.7, 128.4, 128.0, 127.7, 125.6, 125.5, 121.0, 119.1, 114.1, 113.8, 111.0, 107.8, 107.4, 70.4, 53.8, 52.0, 51.8, 49.5, 47.3, 11.2; ESIMS: *m/z* 720 $(M)^+$; HRMS: (ESI *m/z*) for $C_{40}H_{36}ClF_2N_7O_2$ calcd: 720.2665, found: 720.2671 $(M)^+$.

*5.5.11. (R)-3-(4-(4-((5-(4-Chloro-3-fluorophenyl)-2-methyl-1-(4-(trifluoromethoxy)phenyl)-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4k**)*

The compound **4k** was prepared according to the above-described method using **11e** (0.105 g, 0.15 mmol) (yield 0.093 g, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (s, 1H, triazole−*H*), 7.78 (d, 1H, *J* = 7.1 Hz, Ar−*H*), 7.38 (dd, 1H, *J* = 12.0, 1.7 Hz, oxa−Ar−*H*), 7.30−7.23 (m, 2H, Ar−*H*), 7.19−7.14 (m, 2H, Ar−*H*), 7.11−7.06 (m, 2H, oxa−Ar−*H*, Ar−*H*), 7.01 (t, 1H, *J* = 9.0 Hz, oxa−Ar−*H*), 6.95−6.91 (m, 4H, Ar−*H*), 6.82−6.79 (m, 2H, Ar−*H*), 6.36 (s, 1H, pyr−*H*), 5.10−5.00 (m, 1H, oxa−C*H*−), 4.79−4.74 (m, 2H, oxa−CH_2−), 4.13 (dd, 1H, *J* = 6.2, 3.1 Hz, oxa−CH*H*−), 3.88 (dd, 1H, *J* = 6.4, 3.0 Hz, oxa−C*H*H−), 3.47 (s, 2H, pyr−CH_2), 3.10−3.06 (t, 4H, piperazine−*H*), 2.72−2.66 (t, 4H, piperazine−*H*), 2.07 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.6, 167.2, 160.8, 155.8, 148.6, 131.3, 130.1, 129.8, 129.7, 128.8, 128.7, 128.4, 127.1, 125.8, 125.6, 123.6, 121.6, 121.5, 119.2, 115.7, 115.4, 115.1, 114.2, 114.0, 112.3, 110.4, 107.9, 107.6, 105.8, 70.4, 54.0, 52.3, 52.2, 49.9, 47.4, 11.1; ESIMS: *m/z* 804 $(M + H)^+$; HRMS: (ESI *m/z*) for $C_{41}H_{36}ClF_5N_7O_3$ calcd: 804.2488, found: 804.2490 $(M + H)^+$.

*5.5.12. (R)-3-(4-(4-((1-(3,4-Dichlorophenyl)-2-methyl-5-p-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4l**)*

The compound **4l** was prepared according to the above-described method using **11c** (0.097 g, 0.15 mmol) (yield 0.082 g, 73%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H, triazole−*H*), 7.45−7.43 (m, 2H, Ar−*H*) 7.42 (dd, 1H, *J* = 14.6, 2.4 Hz, oxa−Ar−*H*), 7.40 (d, 2H, *J* = 6.7 Hz, Ar−*H*), 7.35−7.27 (m, 3H, Ar−*H*), 7.02 (t, 1H, *J* = 1.9 Hz, oxa−Ar−*H*), 6.97−6.84 (m, 5H, Ar−*H* and 1H, oxa−Ar−*H*), 6.30 (s, 1H, pyr−*H*), 5.08−5.04 (m, 1H, oxa−C*H*−), 4.73−4.08 (m, 2H, oxa−CH_2−), 4.17−4.14 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−CH*H*−), 3.93 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−C*H*H−), 3.65 (s, 2H, pyr−CH_2), 3.14 (t, 4H, piperazine−*H*), 2.83 (t, 4H, piperazine−*H*), 2.27 (s, 3H, Ar−CH_3), 2.11 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.4, 153.3, 148.4, 139.5, 138.2, 136.2, 135.5, 132.1, 131.5, 130.8, 130.1, 128.8, 128.4, 127.0, 127.6, 125.7, 124.4, 123.9, 123.5, 122.1, 121.0, 119.1, 114.2, 111.1, 107.8, 107.4, 70.4, 53.8, 52.1, 51.9, 49.5, 47.3, 30.2, 10.9; ESIMS: *m/z* 750 $(M)^+$; HRMS: (ESI *m/z*) for $C_{41}H_{39}Cl_2FN_7O_2$ calcd: 750.2526, found: 750.2561 $(M)^+$.

*5.5.13. (5R)-3-(4-(4-((1-(2-Bromo-5-fluorophenyl)-5-(2,4-difluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) oxazolidin-2-one (**4m**)*

The compound **4m** was prepared according to the above-described method using **11a** (0.104 g, 0.15 mmol) (yield 0.099 g, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (s, 1H, triazole−*H*), 7.80 (d, 2H, *J* = 7.1 Hz, Ar−*H*), 7.51 (dd, 1H, *J* = 14.6, 2.4 Hz, oxa−Ar−*H*), 7.41 (t, 2H, *J* = 7.1 Hz, Ar−*H*), 7.35−7.31 (m, 1H, Ar−*H*), 7.06 (d, 2H, *J* = 7.8 Hz, Ar−*H*), 7.01−6.93 (m, 2H, Ar−*H* and oxa−Ar−*H*), 6.87 (t, 2H, *J* = 8.9 Hz, oxa−Ar−*H*), 6.34 (s, 1H, pyr−*H*), 5.08−5.04 (m, 1H, oxa−C*H*−), 4.73−4.08 (m, 2H, oxa−CH_2−), 4.17−4.14 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−CH*H*−), 3.93 (dd, 1H, *J* = 6.8, 2.9 Hz, oxa−C*H*H−), 3.65 (s, 2H, pyr−CH_2), 3.11 (t, 4H, piperazine−*H*), 2.77 (t, 4H, piperazine−*H*), 2.02 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 167.9, 162.0, 156.5, 156.2, 155.0, 153.1, 148.6, 146.8, 144.0, 141.0, 137.0, 134.0, 131.1, 130.8, 128.8, 128.7, 125.8, 124.5, 121.0, 120.8, 120.4, 115.5, 113.0, 110.7, 107.8, 107.4, 104.3, 68.1, 53.9, 49.4, 48.0, 47.4, 38.7, 11.0; ESIMS: *m*/*z* 800 $(M)^+$; HRMS: (ESI *m*/*z*) for $C_{40}H_{35}BrF_4N_7O_2$ calcd: 800.1971, found: 800.2000 $(M)^+$.

*5.5.14. (5R)-3-(3-Fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)phenyl)-5-((4-m-tolyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (**4n**)*

The compound **4n** was prepared according to the above-described method using **11h** (0.092 g, 0.6 mmol) (yield 0.074 g, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (s, 1H, triazole−*H*), 7.66 (s, 1H, Ar−*H*), 7.61−7.59 (d, 1H, *J* = 7.8 Hz, Ar−*H*), 7.33−7.29 (t, 1H, *J* = 7.8 Hz, Ar−*H*), 7.17−7.15 (d, 1H, *J* = 7.8 Hz, Ar−*H*), 7.08−7.06 (m, 2H, Ar−*H*), 7.01−6.97 (m, 4H, Ar−*H*), 6.95−6.90 (m, 4H, Ar−*H*), 6.17 (s, 1H, pyr−*H*), 5.10−5.04 (m, 1H, oxa−C*H*−), 4.84−4.73 (m, 2H, oxa−CH_2−), 4.17−4.12 (dd, 1H, *J* = 6.2 Hz, 3.1 Hz, oxa−CH*H*−), 3.93−3.89 (dd, 1H, *J* = 8.7 Hz, oxa−C*H*H−), 3.56 (s, 2H, pyr−CH_2), 3.12−3.10 (t, 4H, piperazine−*H*), 2.74−2.72 (t, 4H, piperazine−*H*), 2.40 (s, 3H, Ar−CH_3), 2.17 (s, 3H, Ar−CH_3), 2.12 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.6, 156.9, 153.4, 148.6, 138.5, 137.3, 134.7, 132.7, 132.3, 131.4, 129.8, 129.6, 129.5, 129.2, 128.7, 127.2, 126.4, 125.0, 122.9, 121.0, 119.2, 115.6, 115.3, 114.2, 111.6, 107.8, 107.5, 70.5, 53.9, 52.2, 51.9, 49.6, 47.4, 31.3, 29.6, 21.3, 20.4, 11.3; ESIMS: *m*/*z* 714 $(M + H)^+$; HRMS: (ESI *m*/*z*) for $C_{42}H_{42}F_2N_7O_2$ calcd: 714.3362, found: 714.3380 $(M + H)^+$.

*5.6. General procedure for the preparation of compounds **5a**–**d***

The compounds (**5a**–**d**) were prepared by acetylation of amino compounds (**12a**–**d**) in the presence of acetyl chloride. In detail, to a stirred solution of appropriate amine (0.15 mmol) in dry dichloromethane (5 mL) at 0 °C, triethylamine (0.3 mmol) was added. Then acetyl chloride (0.2 mmol) was added slowly drop wise. After the addition was complete, the mixture was stirred at room temperature for 1 h under nitrogen atmosphere. After completion of reaction as indicated by TLC, reaction mixture was poured on crushed ice and the product was extracted with dichloromethane (2 × 5 mL). The organic layer was washed with brine, dried (anhydrous Na_2SO_4), solvent was removed under reduced pressure and the product was purified by column chromatography by using chloroform, methanol (10:1) system to give the product.

*5.6.1. N-(((S)-3-(4-(4-((1-(2-Bromo-5-fluorophenyl)-5-(2,4-difluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**5a**)*

The compound **5a** was prepared according to the above-described method using **12a** (0.100 g, 0.15 mmol) (yield 0.091 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50−7.47 (d, 1H, *J* = 2.2 Hz, Ar−*H*), 7.45−7.37 (dd, 1H, *J* = 14.6, 2.4 Hz, oxa−Ar−*H*), 7.40−7.38 (d, 1H, *J* = 2.9 Hz, Ar−*H*), 7.35−7.33 (d, 1H, *J* = 2.2 Hz, Ar−*H*), 7.24−7.21 (d, 1H, *J* = 2.9 Hz, Ar−*H*), 7.04 (d, 1H, *J* = 9.0 Hz, oxa−Ar−*H*), 7.02 (s, 1H, Ar−*H*), 6.89 (t, 1H, *J* = 8.9 Hz, oxa−Ar−*H*), 6.85 (s, 1H, Ar−*H*), 6.21 (d, 1H, *J* = 3.4 Hz, pyr−*H*), 4.78−4.70 (m, 1H, oxa−C*H*−), 4.03−3.97 (dd, 1H, *J* = 9.1, 6.2 Hz, oxa−CH*H*−), 3.76−3.70 (dd, 1H, *J* = 9.1, 6.2 Hz, oxa−C*H*H−), 3.57−3.48 (m, 2H, oxa−CH_2−), 3.47 (s, 2H, pyr−CH_2), 3.09 (t, 4H, piperazine−*H*), 2.74−2.63 (t, 4H, piperazine−*H*), 2.06 (s, 3H, NHCOCH_3), 2.02 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 166.4, 163.3, 160.2, 156.8, 153.2, 134.4, 133.8, 132.5, 130.8, 130.1, 129.2, 128.7, 127.1, 126.0, 125.1, 124.6, 119.1, 116.7, 113.8, 111.8, 107.5, 107.2, 71.8, 53.9, 52.1, 49.9, 47.6, 46.3, 38.6, 22.9, 11.9. ESIMS: *m*/*z* 714 $(M + H)^+$; HRMS: (ESI *m*/*z*) for $C_{34}H_{33}BrF_4N_5O_3$ calcd: 714.1702, found: 714.1676 $(M)^+$.

*5.6.2. N-(((S)-3-(4-(4-((5-(3-Chlorophenyl)-1-(2-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**5b**)*

The compound **5b** was prepared according to the above-described method using **12b** (0.088 g, 0.15 mmol) (yield 0.077 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, 1H, *J* = 2.6 Hz, Ar−*H*), 7.41 (dd, 1H, *J* = 14.6, 2.4 Hz, oxa−Ar−*H*), 7.21 (td, 1H, *J* = 8.8, 1.7 Hz, Ar−*H*), 7.17 (d, 2H, *J* = 5.2 Hz, Ar−*H*), 7.12−7.09 (m, 2H, Ar−*H*), 7.07 (s, 1H, Ar−*H*), 7.02 (dd, 1H, *J* = 8.8 Hz, 2.2 Hz, oxa−Ar−*H*), 6.97−6.94 (d, 1H, *J* = 9.0 Hz, Ar−*H*), 6.90 (dt, 1H, *J* = 6.7, 1.8 Hz, oxa−Ar−*H*), 6.62 (t, 1H, *J* = 5.2 Hz, −N*H*COCH$_3$), 6.39 (s, 1H, pyr−*H*), 4.77−4.68 (m, 1H, oxa−C*H*−), 3.97 (dd, 1H, *J* = 9.0, 6.1 Hz, oxa−CH*H*−), 3.87 (dd, 1H, *J* = 9.1, 6.2 Hz, oxa−C*H*H−), 3.64−3.59 (m, 2H, oxa−CH_2−), 3.47 (s, 2H, pyr−CH_2), 3.15−3.07 (t, 4H, piperazine−*H*), 2.74−2.63 (t, 4H, piperazine−*H*), 2.01 (s, 3H, NHCOCH_3), 1.99 (s, 3H, pyr−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 166.4, 154.3, 153.2, 134.4, 133.8, 132.5, 130.8, 130.7, 130.1, 129.2, 128.7, 127.1, 126.0, 125.1, 124.6, 119.1, 116.7, 116.5, 113.8, 111.8, 107.5, 107.2, 71.8, 53.9, 52.1, 49.9, 47.6, 46.3, 38.6, 22.9, 11.9. ESIMS: *m*/*z* 634 $(M + H)^+$; HRMS: (ESI *m*/*z*) for $C_{34}H_{35}ClF_2N_5O_3$ calcd: 634.2396, found: 634.2425 $(M + H)^+$.

*5.6.3. N-(((S)-3-(4-(4-((1-(2,4-Difluorophenyl)-5-(4-isopropylphenyl)-2-methyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**5c**)*

The compound **5c** was prepared according to the above-described method using **12c** (0.092 g, 0.15 mmol) (yield 0.084 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40 (m, 1H, Ar−*H* and 1H, oxa−Ar−*H*), 7.12 (dd, 1H, *J* = 3.0, 8.03 Hz, Ar−*H*), 7.05−6.99 (m, 3H, Ar−*H* and 1H, oxa−Ar−*H*), 6.97−6.85 (m, 2H, Ar−*H* and 1H, oxa−Ar−*H*), 6.33 (s, 1H, pyr−*H*), 6.22−6.19 (t, 1H, *J* = 5.2, NH), 4.78−4.70 (m, 1H, oxa−C*H*−), 4.00 (dd, 1H, *J* = 6.1 Hz, 9.0 Hz, oxa−CH*H*−), 3.73 (dd, 1H, *J* = 9.1, 6.2 Hz, oxa−C*H*H−), 3.67−3.62 (m, 2H, oxa−CH_2−), 3.54 (s, 2H, pyr−CH_2), 3.09 (t, 4H, piperazine−*H*), 2.87−2.78 (m, 1H, CH$_3$−C*H*−CH$_3$), 2.74−2.63 (t, 4H, piperazine−*H*), 2.06 (s, 3H, NHCOCH_3), 1.99 (s, 3H, pyr−CH_3), 1.20−1.18 (d, 6H, *J* = 6.9 Hz, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 166.4, 154.3, 153.2, 152.2, 133.8, 132.5, 130.8, 130.7, 130.1, 128.2, 128.7, 127.5, 126.0, 125.1, 124.6, 120.1, 115.7, 111.8, 107.5, 107.2, 71.8, 53.9, 52.1, 49.9, 47.6, 46.3, 38.6, 30.2, 23.3, 22.9, 13.9. ESIMS: *m*/*z* 660 $(M + H)^+$; HRMS: (ESI *m*/*z*) for $C_{37}H_{41}F_3N_5O_3$ calcd: 660.3161, found: 660.3145 $(M + H)^+$.

*5.6.4. N-(((S)-3-(3-Fluoro-4-(4-((1-(4-fluorophenyl)-2-methyl-5-o-tolyl-1H-pyrrol-3-yl)methyl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (**5d**)*

The compound **5d** was prepared according to the above-described method using **12d** (0.085 g, 0.15 mmol) (yield 0.081 g, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43 (dd, 1H, *J* = 14.5, 3.0 Hz, oxa−Ar−*H*), 7.06 (s, 2H, Ar−*H*), 7.01−6.98 (m, 4H, Ar−*H* and 1H, oxa−Ar−*H*), 6.95−6.92 (m, 2H, Ar−*H* and 1H, oxa−Ar−*H*), 6.43−

6.32 (bs, 1H, –N*H*COCH$_3$), 6.20 (s, 1H, pyr–*H*), 4.78–4.72 (m, 1H, oxa–C*H*–), 3.99 (dd, 1H, J = 6.1, 9.0 Hz, oxa–CH*H*–), 3.76–3.73 (m, 3H, oxa–C*H*$_2$–, oxa–C*H*H–), 3.67–3.59 (t, 4H, piperazine–*H*), 3.47 (s, 2H, pyr–C*H*$_2$), 3.26–3.24 (t, 4H, piperazine–*H*), 2.15 (s, 3H, –NHCOC*H*$_3$), 2.12 (s, 3H, Ar–C*H*$_3$), 2.01 (s, 3H, pyr–C*H*$_3$); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 171.5, 166.4, 154.3, 153.2, 134.4, 133.8, 132.5, 130.8, 130.3, 129.2, 128.7, 127.1, 126.0, 125.1, 124.6, 119.0, 116.7, 113.8, 111.8, 107.5, 107.2, 71.7, 53.5, 52.3, 50.1, 47.6, 46.3, 38.6, 22.8, 22.0, 11.9; ESIMS: m/z 614 $(M + H)^+$; HRMS: (ESI m/z) for $C_{35}H_{38}F_2N_5O_3$ calcd: 614.2942, found: 614.2950 $(M + H)^+$.

5.7. Antimycobacterial assay

The antimycobacterial activities of novel diarylpyrrole–oxazolidinone conjugates **4a**–**n** and **5a**–**d** were evaluated against *M. tuberculosis* H37Rv, *M. tuberculosis* Rif^R and *M. tuberculosis* XDR-1 using microplate dilution assay [28,29]. All the compounds were initially screened against *M. tuberculosis* H$_{37}$Rv at the single concentration of 32 μg/mL in triplicate in a microtiter plate. The active compounds from this screening were further tested for Minimum Inhibitory Concentration (MIC) determination using the broth microdilution assay. The microtiter plates were incubated for 2–3 weeks at 37 °C in CO_2 incubator and read visually for the absence of growth turbidity.

5.8. Cytotoxicity assay

The potent compounds (**4b**–**f**, **4i** & **5c**) were evaluated for cytotoxic effect on mouse macrophage (J-774) cell lines using MTT assay, in a 96 well plate format [30]. Cells were incubated in Rosewell Park Memorial Institute (RPMI) containing 10% fetal calf serum (FCS) with the test material (40 μg/ml) for 24 h at 37 °C in CO_2 incubator. After the completion of incubation 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added and cells were further incubated for 3 h at 37 °C in CO_2 incubator. Formation of formazan salt by mitochondrial dehydrogenases and was determined by Elisa reader at 450 nm (Multiskan Spectrum; Thermo Electron Corporation, USA). The percentage cytotoxicity was calculated with respect to the untreated cells.

5.9. Antibacterial assay

All the test compounds were dissolved in DMSO of 2 mg/mL. Empty sterilized disks of 6 mm were impregnated with compounds in the range from 1 to 80 μg/disk and placed in triplicate in the medium inoculated with fresh bacteria ($1–2 \times 104$ cfu mL^{-1}) on the freshly prepared sterile Mueller Hinton agar plates [31]. The plates were incubated at 35 °C for 24 h for zone of inhibition, if any, around the disks. Lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate was considered to be minimum inhibitory concentrations. DMSO (20 μL) loaded in agar disc was used as negative control. Linezolid was used as positive control.

5.10. Material and methods used in docking studies

Geometry optimization for all molecules was performed by Gaussian 09 using PM3 semi-empirical method [32]. The structure of 50S unit obtained from Protein Data Bank (PDB ID: 3CPW at 2.7 Å resolution) [14]. Crystal structure was prepared using protein preparation wizard in Schrodinger 2012 [33]. Docking studies were performed using Gold docking software. Images were taken using Pymol visualization software [34].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.03.027.

References

[1] World Health Organization, 47th World Health Assembly: Provisional Agenda Item 19, Tuberculosis-Progress Report by the Director General, Document WHA47/1994/A47/12, Geneva, Switzerland, 1994.
[2] World Health Organization, Global Tuberculosis Control: WHO Report, 2011. Further info at the web site: http://www.who.int/gtb/.
[3] World Health Organization, Global Tuberculosis Control: Surveillance, Planning, Financing, WHO Report 2004, Geneva, Switzerland, 2004.
[4] J.P. Cegielski, D.P. Chin, M.A. Espinal, T.R. Frieden, R. Rodriquez Cruz, E.A. Talbot, D.E. Weil, R. Zaleskis, M.C. Raviglione, The global tuberculosis situation. Progress and problems in the 20th century, prospects for the 21st century, Infect. Dis. Clin. North Am. 161 (2002) 1–58.
[5] T.R. Frieden, S.S. Munsiff, The DOTS strategy for controlling the global tuberculosis epidemic, Clin. Chest Med. 26 (2005) 197–205.
[6] J.D. Mckinney, W.R.J. Jacobs, B.R. Bloom, R.M. Krause (Eds.), Academic Press, New York, 1998, pp. 51–146.
[7] H. Tomioka, Curr. Pharm. Des. 12 (2006) 4047–4070.
[8] D. Maher, M. Raviglione, Clin. Chest Med. 26 (2005) 168–182.
[9] L.G. Dover, G.D. Coxon, J. Med. Chem. 54 (2011) 6157–6165.
[10] N. Pandit, R.K. Singla, B. Shrivastava, Int. J. Med. Chem. (2011) 1–24. (Article ID 159285).
[11] M.R. Sarbachyn, C.W. Ford, Angew. Chem. Int. Ed. 42 (2003) 2010–2030.
[12] J.C. Rodriguez, M. Ruiz, M. Lopez, G. Royo, Int. J. Antimicrob. Agents 20 (2002) 464–467.
[13] S.J. Brickner, M.R. Barbachyn, D.K. Hutchinson, P.R. Manninen, J. Med. Chem. 51 (2008) 1981–1990.
[14] J.A. Ippolito, Z.F. Kanyo, D. Wang, F.J. Franceschi, P.B. Moore, T.A. Steitz, E.M. Duffy, J. Med. Chem. 51 (2008) 3353–3356.
[15] O.A. Phillips, E.E. Udo, A.A.M. Ali, N. Al-Hassawi, Bioorg. Med. Chem. 11 (2003) 35–41.
[16] O.A. Phillips, E.E. Udo, A.A.M. Ali, S.M. Samuel, Bioorg. Med. Chem. 13 (2005) 4113–4123.
[17] F. Reck, F. Zhou, M. Girardot, G. Kern, C.J. Eyermann, N.J. Hales, R.R. Ramsay, M.B. Gravestock, J. Med. Chem. 48 (2005) 499–506.
[18] T. Komine, A. Kojima, Y. Asahina, T. Saito, H. Takano, T. Shibue, Y. Fukuda, J. Med. Chem. 51 (2008) 6558–6562.
[19] D. Deidda, G. Lampis, R. Fioravanti, M. Biava, G.C. Porretta, S. Zanetti, R. Pompei, Antimicrob. Agents Chemother. 42 (1998) 3035–3037.
[20] M. Biava, G.C. Porretta, G. Poce, S. Supino, D. Deidda, R. Pompei, P. Molicotti, F. Manetti, M. Botta, J. Med. Chem. 49 (2006) 4946–4952.
[21] A. Kamal, R.V.C.R.N.C. Shetti, S. Azeeza, S.K. Ahmed, P. Swapna, A.M. Reddy, I.A. Kahn, S. Sharma, S.T. Abdullah, Eur. J. Med. Chem. 45 (2010) 4545–4553.
[22] A. Kamal, R.V.C.R.N.C. Shetti, S. Azeeza, P. Swapna, M.N.A. Khan, A.M. Reddy, I.A. Kahn, S. Sharma, S.T. Abdullah, Eur. J. Med. Chem. 46 (2011) 893–900.
[23] A. Kamal, K.S. Reddy, S.K. Ahmed, M.N.A. Khan, R.K. Sinha, J.S. Jadav, S.K. Arora, Bioorg. Med. Chem. 14 (2006) 650–658.
[24] S.J. Brickner, D.K. Hutchinson, M.R. Barbachyn, P.R. Manninen, D.A. Ulanowicz, S.A. Garmon, K.C. Grega, S.K. Hendges, D.S. Toops, C.W. Ford, G.E. Zurenko, J. Med. Chem. 39 (1996) 673–679.
[25] M.R. Barbachyn, D.K. Hutchinson, S.J. Brickner, M.H. Cynamon, J.O. Kilburn, S.P. Klemens, S.E. Glickman, K.C. Grega, S.K. Hendges, D.S. Toops, C.W. Ford, G.E. Zurenko, J. Med. Chem. 39 (1996) 680–685.
[26] H.C. Kolb, M.G. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. 40 (2001) 2004–2021.
[27] F. Pagliai, T. Pirali, E.D. Grosso, R.D. Brisco, G.C. Tron, G. Sorba, A.A. Genazzani, J. Med. Chem. 49 (2006) 467–470.
[28] R. Maccari, R. Ottana, F. Monforte, M.G. Vigorita, Antimicrob. Agents Chemother. 46 (2002) 294–299.
[29] R.J. Wallace, D.R. Nash, L.C. Steele, V. Steingrube, J. Clin. Microbiol. 24 (1986) 976–981.
[30] I. Orme, J. Secrist, S. Anathan, C. Kwong, J. Maddry, R. Reynolds, A. Poffenberger, M. Michael, L. Miller, J. Krahenbuh, L. Adams, A. Biswas, S. Franzblau, D. Rouse, D. Winfield, J. Brooks, Antimicrob. Agents Chemother. 45 (2001) 1943–1946.
[31] National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, NCCLS Document M7-A4, fourth ed., National Committee for Clinical Laboratory Standards, Villanova, PA, 1997.

[32] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.J.A. Montgomery, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision B.1, Gaussian, Inc., Wallingford, CT, 2010.
[33] Maestro, Version 9.3, Schrödinger, LLC, New York, NY, 2012.
[34] The PyMOL Molecular Graphics System, Version 1.5.0.4, Schrödinger, LLC, 2012.